UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/523,835	02/07/2005	Francis Ignatious	P51366	2405

20462 7590 06/03/2009

SMITHKLINE BEECHAM CORPORATION
CORPORATE INTELLECTUAL PROPERTY-US, UW2220
P. O. BOX 1539
KING OF PRUSSIA, PA 19406-0939

EXAMINER	
PHILLIPS JR, WELDON P	

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
06/03/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

US_cipkop@gsk.com

Office Action Summary	Application No.	Applicant(s)	
	10/523,835	IGNATIOUS ET AL.	
	Examiner	Art Unit	
	WELDON P. PHILLIPS JR.	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-46* is/are pending in the application.

4a) Of the above claim(s) *4,5,7,13,14,23 and 25-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,6,8-12,15-22 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *02/07/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

This application for patent entered the national stage under 35 U.S.C. 371 on February 7, 2005 from PCT/US2003/24641, filed August 7, 2003, which claims benefit from U.S. Provisional Application 60/401,726, filed August 7, 2002.

Applicant's claim for the benefit of said prior-filed U.S. Provisional Application under 35 U.S.C. 119(e) is acknowledged. Based on the examiner's review of U.S. Provisional Application 60/401,726, said provisional application does not provide support for the surfactant species of claim 9, "sorbitan esters and sorbitan fatty acids," the species of polymeric carriers recited in claims 15, 36 and 43 including the currently elected species of polymeric carrier, Eudragit L 100-55, and the currently elected species of active agent, (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-{4-[(2-methyl-1,3-thiazol-4-yl)methoxy]benzyl}propylcarbamate, which is the last species recited in claim 17.

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) since applicant does not have full support for the instant claims. The limitations for which examiner did not find support in the Provisional Application are indicated above. If applicant believes the examiner is in error, applicant should direct the examiner to where support for the limitations may be found.

In light of the species elections in the present application, no claims receive the benefit of an earlier filing date and the filing date for purposes of applying prior art is August 7, 2003.

Claim Status

Claims 1 and 3-46, as amended on April 16, 2009 are pending.

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on April 16, 2009 is acknowledged. The traversal is on the ground(s) that no lack of unity was found by the examiner in the PCT receiving office, while questioning examiner's requirement for restriction to a single invention among Groups I, II and III, and indicating all the claims are the result of a common research and development effort and should be examined together. Applicant's argument is not found persuasive.

The issue when examining a national stage application entering the United States under 35 U.S.C. 371 is whether the groups of inventions are so linked as to form a single general inventive concept ("requirement of unity of invention") under PCT Rule 13.1. As stated in Rule 13.2, where a group of inventions is claimed in an international application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features, where special technical features are "those technical features that define a contribution which each of the claimed inventions,

considered as a whole, makes over the prior art." In the instant application, the examiner indicated the special technical feature shared by Groups I, II and III was an electrospun fiber comprising a pharmaceutically acceptable polymer and an amorphous form of a pharmaceutically active agent and that previously presented claim 28 of the instant application does not present a contribution over the prior art in light of claim 24 of Ignatious (WO 01/54667). By definition, if a claim in one of applicant's groups is anticipated and/or obviated by the prior art, then whatever technical feature which may be shared amongst the groups of that application does not provide a contribution over the prior art under PCT Rule 13.2, unity between each of the groups of inventions is broken and restriction to one group of invention may be required. Finally, it should be apparent from the above that whether the claims are the result of a common research and development effort is irrelevant to the issue of whether or not the claims may be restricted to one invention. For these reasons, the requirement is still deemed proper and is therefore made **FINAL**.

Applicant's elections with traverse of Eudragit L 100-55 as the single species of polymeric carrier present in the composition, (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-{4-[(2-methyl-1,3-thiazol-4-yl)methoxy]benzyl}propylcarbamate as the single active agent present in the composition and for the presence of a surfactant in the composition in the reply filed on April 16, 2009 is also acknowledged. Applicant failed to elect for a species of surfactant present in the composition as required by the examiner's species election, but in the interest of moving prosecution forward in the instant application, that portion

of the species election is lifted. Unless otherwise indicated in this action, the examination of the claims is based solely on applicant's election of the above identified species. The traversal is on the ground(s) that each chemical species is not a distinct chemical with distinct chemical moieties as it applies to the special technical features herein. In the absence of a statement that the species of the invention are obvious variants, applicant's argument is not found persuasive.

With respect to the species requirement, the examiner notes that there are multiple species of divergent active agents and polymeric carriers present in the claims of the instant application. As such, there are several classifications and subclasses involved for the diverse species of claimed active agents and polymeric carriers. More specifically, and as stated in the restriction requirement dated March 25, 2009, this application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1 as described above in light of e.g., claims 24 and dependent claims of the Ignatious patent document discussed supra which further recites a plurality of polymeric carriers and active agents present in the instant claims. In addition, the claimed polymeric carriers and active agents require different search strategies and search terms and raise different prior art and non-prior art issues. Add to that the various and divergent genera and species recited, e.g., polyvinyl alcohol vs. hydroxypropylmethylcellulose vs. polyacrylates as polymeric carriers and aspirin vs. carvedilol vs. (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-{4-

[(2-methyl-1,3-thiazol-4-yl)methoxy]benzyl}propylcarbamate as active agents, in claims 9, 13-17, 34-38 and 41-45, and it would constitute an undue burden on the examiner if either the restriction requirement or species election were lifted at this time. For these reasons, the requirement is still deemed proper and is therefore made **FINAL.**

Pursuant to applicant's response dated April 16, 2009, claims 4, 5, 7, 14, 23, 25-38 and 40-45 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected Groups, there being no allowable generic or linking claim.

> *REMINDER: Although withdrawn, claims 26 and 27 are "use claims," which can reasonably be interpreted as claims to products, method of making and methods of using. As such, they are subject to 35 U.S.C. 101 and 35 U.S.C. 112, 2nd Paragraph rejections. Applicant is directed to cancel or amend claims 26 and 27 to remove the "use claim" language.*

For the reasons cited below, applicant's withdrawal of claims 13, 39 and 46 is improper. As to claim 13, the specification of the instant application makes clear the Eudragit family of polymers, including the elected species, Eudragit L 100-55, is a polyacrylate, a subgenus present in claim 13 (p. 10, lines 16-17 of specification). As to claims 39 and 46, both are product-by-process claims, which the examiner placed in Group I in the restriction requirement dated March 25, 2009 and asserts should properly be examined with the composition claims of Group I. As such, claims 13, 39 and 46 are not currently withdrawn and are examined herein. Applicant traversed the restriction/election requirements in the reply filed on April 16, 2009.

Acknowledgement

Copies of the International Search Report and International Preliminary Report on Patentability have been received/obtained by the examiner and their contents have been considered.

Information Disclosure Statement

One Information Disclosure Statement (IDS) was filed by applicant on February 7, 2005 in compliance with 37 CFR § 1.97, 37 CFR § 1.98 and MPEP § 609. The contents of said IDS were considered by the examiner in full.

Claim Rejections – 35 USC 112 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 6, 8-13, 15-22, 24, 39 and 46 are rejected under 35 USC 112 second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as their invention.

Claim 1, dependent claims 3, 6, 8-13, 15-22 and 24, and product-by-process claims 39 and 46, which depend from process claims producing formulations "according to claim 1," recite the limitation "homogeneously." "Homogeneously" is a term of degree. The instant specification provides no indication how, what, when or where the integration of a polymeric carrier by an amorphous form of a pharmaceutically acceptable active agent might be measured and deemed homogeneous or not homogeneous. Terms of degree are indefinite when the specification contains no

"explicit guidelines" to distinguish from things which are not so. Ex parte Oetiker, 23 USPQ2d 1651, 1655 (1990) and Ex parte Oetiker, 23 USPQ2d 1641 and Seattle Box Co. v. Industrial Crating & Packaging, Inc. 221 USPQ 568, 574. The examiner has considered claim 1 as a whole, in light of the specification and the teachings of the prior art, and decided after careful consideration that claim 1 does not apprise "one of ordinary skill in the art of its scope and, therefore, [does not] serve ... the notice function required by 35 U.S.C. 112, second paragraph, by providing clear warning to others as to what [would] constitute infringement of the patent. See, e.g., Solomon v. Kimberly-Clark Corp., 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000). As such, claims 1, 3, 6, 8-13, 15-22, 24, 39 and 46 are not clear or precise with respect to their characterization of "homogeneously" raising a question as to the metes and bounds of the claims and the scope of the patent protection sought by applicant.

Claim 1, dependent claims 3, 6, 8-13, 15-22 and 24, and product-by-process claims 39 and 46, which depend from process claims producing formulations "according to claim 1," recite the limitation "stable." "Stable" is a term of degree. While the Examples section of the instant specification provides a set of conditions under which one might begin to assess the stability of an amorphous form of an active agent in a formulation (p. 16, line 25-35), there is no indication in the description how and when the stability of an amorphous form of an active agent in a formulation would be deemed stable or not stable, e.g., what amount of deviation from amorphous state over what period of time would give rise to a finding of stable or not stable? Terms of degree are indefinite when the specification contains no "explicit guidelines" to distinguish from

things which are not so. Ex parte Oetiker, 23 USPQ2d 1651, 1655 (1990) and Ex parte Oetiker, 23 USPQ2d 1641 and Seattle Box Co. v. Industrial Crating & Packaging, Inc. 221 USPQ 568, 574. The examiner has considered claim 1 as a whole, in light of the specification and the teachings of the prior art, and decided after careful consideration that claim 1 does not apprise "one of ordinary skill in the art of its scope and, therefore, [does not] serve ... the notice function required by 35 U.S.C. 112, second paragraph, by providing clear warning to others as to what [would] constitute infringement of the patent. See, e.g., Solomon v. Kimberly-Clark Corp., 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000). As such, claim 1, 3, 6, 8-13, 15-22, 24, 39 and 46 are not clear or precise with respect to their characterization of "stable" raising a question as to the metes and bounds of the claims and the scope of the patent protection sought by applicant.

Claims 16 and 17 recite the limitation "drug substance." There is insufficient antecedent basis for this limitation in the claim, as claim 1 and the remainder of the claims utilize the claim limitation "active agent." The examiner has considered claim 16 and 17 as a whole, in light of the specification and the teachings of the prior art, and decided after careful consideration that claim 8 does not apprise "one of ordinary skill in the art of its scope and, therefore, [does not] serve ... the notice function required by 35 U.S.C. 112, second paragraph, by providing clear warning to others as to what [would] constitute infringement of the patent. See, e.g., Solomon v. Kimberly-Clark Corp., 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000). As such, claims 16 and 17 are not clear or precise with respect to its characterization of "drug substance" raising a

question as to the metes and bounds of the claim and the scope of the patent protection sought by applicant.

For purposes of examination, the examiner has interpreted the limitation "drug substance" in claims 16 and 17 to read "active agent."

Claims 9 and 15 recite the limitations "Triton X-200" and numerous "Eudragit" polymers, all of which are trademarked products. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of the 35 U.S.C. 112, second paragraph. Ex parte Simpson, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. In fact, the value of a trademark would be lost to the extent that it became descriptive of a product, rather than used as an identification of a source or origin of a product. Thus, the use of a trademark or trade name in a claim to identify or describe a material or product would not only render a claim indefinite, but would also constitute an improper use of the trademark or trade name. MPEP § 2173.05(u). In the instant case, the claim language "Triton X-200" and "Eudragit ..." identifies particular materials or products. Therefore, claims 9 and 15 are indefinite and do not apprise "one of ordinary skill in the art of [their] scope and, therefore, [do not] serve ... the notice function required by 35 U.S.C. 112, second paragraph, by providing clear warning to others as to what [would] constitute infringement of the patent. See, e.g., Solomon v. Kimberly-Clark Corp., 216 F.3d 1372, 1379, 55 USPQ2d 1279, 1283 (Fed. Cir. 2000). As such, claims 9 and 15 are not clear or precise with respect to the use of the claim

language "Triton X-200" and the numerous "Eudragit" polymers raising a question as to the metes and bounds of the claims and the scope of the patent protection sought by applicant.

Claim Rejections – 35 USC 112 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 6, 8-13, 15-22, 24, 39 and 46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1, and dependent claims 3, 6, 8-13, 15-22, 24, 39 and 46, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for "[a] pharmaceutical composition comprising an electrospun fiber of a pharmaceutically acceptable amorphous polymeric carrier homogeneously integrated with an amorphous form of a pharmaceutically acceptable active agent," does not reasonably provide enablement for "[a] pharmaceutical composition comprising an electrospun fiber of a pharmaceutically acceptable amorphous polymeric carrier homogeneously integrated with a *stable* amorphous form of a pharmaceutically acceptable active agent." Based on the current record, applicant has not has not enabled the full scope of these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (Wands, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." Wands, 8 USPQ2d 1404. Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a prima facie case is discussed below.

(1 & 2) The nature of the invention and breadth of the claims:

The claims are drawn to compositions comprising electrospun fibers of amorphous polymeric carriers known in the art, e.g., the elected species Eudragit L 100-55, homogeneously integrated with a stable amorphous form of a pharmaceutically acceptable active agent, e.g., the elected species (3R,3aS,6aR)-hexahydrofuro[2,3-

b]furan-3-yl (1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-{4-[(2-methyl-1,3-thiazol-4-yl)methoxy]benzyl}propylcarbamate, further comprising a surfactant. In construing the claims, the claims are narrowly drawn in terms of how the compositions may be formulated, e.g., electrospun fibers of a polymeric carrier and a active agent +/- a surfactant.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Amorphous formulations of hundreds, if not thousands, of pharmaceutical formulations are known and a number of means for producing said amorphous formulations including milling, solvent precipitation, vapor condensation, spray drying and freeze drying are also known (Hancock, J. Pharmaceut. Sci. 86, 1-12 (1997), p. 1, col. 1, para. 1 and Fig. 1). Amorphous formulations are appreciated in the pharmaceutical arts for their enhanced dissolution profiles and the increased bioavailability of active agents (Kawakami, J. Pharmaceut. Sci. 94, 948-965 (2005), p. 948, para. 1). Although amorphous formulations may be desirable, there are a number of difficulties associated with their use and formulation. Most importantly, amorphous materials are thermodynamically *unstable*, possessing higher enthalpies, specific volumes, molecular motion, entropy and chemical reactivities than their corresponding thermodynamically *stable* crystalline formulations, and tend to relax toward a quasi-equilibrium/metastable state in a thermodynamic effort to revert to their thermodynamically desirable crystalline form over time, even below the glass transition temperature, T_g (Hancock, all of p. 2 and Fig. 2; Kawakami, p. 949, para. 1 and p. 950, Fig. 1; Craig, Int. J. of Pharmaceut. Sci. 179-207 (1999), p. 180, para. 2 and p. 181, Fig.

1). No theory accounts for all of the thermodynamic properties or changes seen at the glass transition temperature in these systems (Hancock, p. 2, col. 2, para. 1 and Kawakami, p. 949, para. 1, Craig, p. 182, para. 1), our understanding of these systems remains incomplete and predictability with respect to the thermodynamic and chemical properties of amorphous formulations, which includes their stability, remains elusive.

(5) The relative skill of those in the art:

The relative level of skill in pharmaceutical formulation arts is high. Although research efforts have been directed at understanding the thermodynamic and physical properties of amorphous systems for decades, a thorough understanding of the thermodynamic properties of amorphous systems remains an area of intensive research efforts.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification provides basic teachings, by way of a number of Examples, on formulating pharmaceutical compositions comprising electrospun fibers of amorphous polymeric carriers and active agents known in the art, including one example with the elected polymeric carrier species, Eudragit L 100-55, with amorphous forms of pharmaceutically acceptable active agents, including the elected species of active agent, (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-{4-[(2-methyl-1,3-thiazol-4-yl)methoxy]benzyl}propylcarbamate, including a surfactant. The stability over time of two pharmaceutical compositions comprising electrospun fibers of non-elected species

were assessed over time up to 161 days by x-ray powder diffraction (XRPD) (see Fig. 2 and 4), a methodology known in the art for assessing the crystalline character in an amorphous formulation and a plurality of other formulations were assessed for amorphous morphology by XRPD or modulated differential scanning calorimetry (MDSC). However, the specification lacks a clarification concerning what is meant by stability of an amorphous form of a pharmaceutically acceptable active agent and does not clarify what the sensitivity of the practiced XRPD method is to crystalline formation. Furthermore, it is unclear what the impact of an inherently amorphous polymeric carrier on the ability of this method to discern changes in the structural characteristics of the active agent or what the impact of the nanofibrous character of the samples has on XRPD or MDSC methodologies. Finally, no indication of the stability or lack thereof of the electrospun fibers comprising Eudragit L 100-55, (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-{4-[(2-methyl-1,3-thiazol-4-yl)methoxy]benzyl}propylcarbamate, either with or without a surfactant are reported.

(8) The quantity of experimentation necessary:

Considering the lack of thermodynamic stability known in the pharmaceutical formulation arts to be associated with amorphous formulations, the relative nature of the claim limitation "stable," the lack of clarification regarding the use of this claim limitation means, which when used as an adjective implies firmly established, fixed, steadfast, not changing, not fluctuating, unvarying, permanent or enduring (http://www.merriam-webster.com/dictionary/stable[3]), the term "stable" should not be applied without

qualification to pharmaceutical compositions comprising amorphous formulations. Because these systems are by definition thermodynamically unstable, transitioning to their relaxed or metastable stable in an effort to revert to their thermodynamically desirable crystalline form over time, even below the glass transition temperature, T_g, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate with the scope of the claims. As such, claim 1, and dependent claims 3, 6, 8-13, 15-22 and 24, contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the full scope of the invention.

Claim Rejections – 35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham v. John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 3, 6, 8-13, 15-22, 24, 39 and 46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ignatious [WO 01/54667 (2001), see PTO-892 dated March 25, 2009], in view of Pendyala [WO 02/56867 (2002), see PTO-892], Hale [WO 00/76961 (2000), see PTO-892] and Verreck [Preparation and characterization of nanofibers containing amorphous drug dispersions generated by electrostatic spinning, Pharmaceut. Res. 20, 810-817 (2003), see IDS dated February 7, 2005], as evidenced by the Chemical Abstract Service entry for CAS 313682-08-5 [see PTO-892], Encyclopedia Britannica Online entry for Chemistry of Industrial Polymers, see [PTO-892] and Mehta [Release performance of a poorly soluble drug from a novel, Eudragit-based multi-unit erosion matrix, Int. J. Pharmaceut. 213, 7-12 (2001), see PTO-892].

The Ignatious patent document teaches pharmaceutical composition comprising an electrospun fiber of a pharmaceutically acceptable polymeric carrier integrated with a

pharmaceutically acceptable active agent (claim 1); wherein Example 12 describes elecrospun fibers comprising eutectic formulations, suggestive of the presence of glassy or amorphous formulations of active agent based on MDSC data when the concentrations of the active agent in the formulations is approximately 30% within a polyethylene oxide polymer, a polymer not considered an amorphous polymer due to its repeating subunits and which, not surprisingly, retains its melting endotherm in these formulations (p. 22, Example 12); wherein a preferable embodiment is that the active agent is integrated in a homogeneous manner (para. bridging p. 4-5); wherein the active agent is nanoparticle in size (claim 2), which is an expected property since the fibers produced by electrospinning are nanofibers with diameters measured in nanometers, in the range of 100 nM (p. 5, lines 5-6 and 33-35); wherein the active agent may be only sparingly soluble (claim 5); wherein the polymeric carrier may be water insoluble (claim 7); wherein the composition further comprises a surfactant (claim 8); wherein the composition may further comprise a surface active agent or surfactant, including a plurality of those present in claim 9, which may be present in amounts of about 10% w/w of the drug composition, which due to the "about" language can reasonable be interpreted to mean 5 to 15% w/w of the drug composition (p. 16, lines 2-5); wherein the composition further comprises an absorption enhancer (claim 9); wherein the composition provides a taste-masking effect on the active agent (claim 10); wherein polyacrylates and their derivatives such as the Eudragit family of polymers available from Rohm Pharma are suitable polymeric carriers for these pharmaceutical compositions (p. 11, lines 29-30); wherein the active agent may be any number of

classes of agents including an antiviral agent like the elected species of active agent (claim 13); wherein the active agents were electrospun into fibers on a w/w basis of about 12% to 80% and those that were tested for drug content post-spinning were found to have a drug content that generally corresponded to the w/w ratio prior to electrospinning (Examples 1-21). With respect to differences in % w/w of polymeric carrier, the examiner notes that generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955).

The Ignatious patent document further teaches that the composition is intended for oral administration (claim 17); wherein the active agent demonstrates improved bioavailability (claim 18) or has modified release profile (claims 22 and 23); wherein the electrospun fiber is encapsulated or compressed into a tablet (claim 19); wherein the composition is further ground, which in the pharmaceutical arts inherently means to reduce the size of the components for incorporation into suitable dosage forms (claim 20); and wherein the composition provides for controlled release, sustained release, or pulsatile release of the active agent from the composition (claim 22), which would be expected from the polyacrylate Eudragit family of polymeric carriers which are taught as water insoluble polymers (p. 13, lines 5-8), useful for providing for controlled release of

active agents and that pH-sensitive polyacrylate containing polymers can even be useful in providing for pulsatile release profiles as well (p. 12, line 2-8).

Although the Ignatious patent document teaches that the polyacrylates and their derivatives such as the Eudragit family of polymers available from Rohm Pharma are suitable polymeric carriers for these pharmaceutical compositions, the Ignatious patent document does not teach the applicant's elected species of Eudragit L 100-55. The Pendyala patent document addresses this shortcoming. The Pendyala patent document teaches that the efficacy of many antibiotics depends solely upon the time of exposure of microorganisms above the minimum inhibitory concentration rather than peak serum concentrations (p. 2, lines 1-5); that a promising approach for achieving the aforementioned results involves optimizing an antibiotic's release profile such that the total dose is released within the time of transit through the absorption window (p. 4, lines 1-9); wherein the pharmaceutical compositions comprises a polymeric carrier such as methacrylic acid - ethylacrylate co-polymer sold commercially as Eudragit L 100-55 (p. 6, lines 15-17); wherein the composition may be formulated into granules for capsules or pressed into tablets, providing for a modified release profile, e.g., controlled, extended or sustained release, that maximizes bioavailability, enhances therapeutic response, reduces dosing frequency, improves patient compliance and reduces local side effects by maintaining active agent concentrations within therapeutic ranges that selectively elicit desired therapeutic benefits over an extended period of time when compared with conventional dosage forms (p. 8, lines 1-18).

While the Ignatious patent teaches pharmaceutical compositions comprising antiviral agents, the Ignatious and Pendyala patent documents do not teach the elected species of active agent, (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl (1S,2R)-3-[(1,3-benzodioxol-5-ylsulfonyl)(isobutyl)amino]-2-hydroxy-1-{4-[(2-methyl-1,3-thiazol-4-yl)methoxy]benzyl}propylcarbamate, which the examiner asserts is more commonly known as brecanavir (STN entry for brecanavir, CAS 313682-08-5). The Hale patent document addresses this shortcoming. The Hale patent document teaches a class of sulfonamide human immunodeficiency virus (HIV) aspartyl protease inhibitors, among them brecanavir (p. 52 and 307, compound 368), which is claimed as one of the preferred embodiments of the invention in claims 15-17, the latter of which is composed only eight most preferred species (p. 382); wherein brecanavir is demonstrated to have promising antiviral activity (based upon EC_{50}s) against wild-type HIV and two protease cocktail-resistant strains of HIV on the order of less than 1 nM for the wild-type strain and one strain of the protease-cocktail resistant virus and less than 10 nM for the other protease cocktail-resistant strain (p. 359-360 and 366), whereas the inhibitory concentrations of 5 other well known and clinically-relevant protease cocktail inhibitors ranges between 690 nM and 1 μM concentrations for both resistant strains (p. 360). With respect to the physical properties of brecanavir which entered the STN database on January 12, 2001, brecanavir would be predicted to have water solubility of 0.0052 g/L or less, depending on the pH (STN entry for brecanavir, CAS 313682-08-5), satisfying the sparingly soluble claim limitation of claim 6 with respect to the active agent brecanavir.

Although the Ignatious patent documents teaches electrospinning fibers comprising eutectic mixtures of polymeric carrier and active agent, suggestive of glassy or amorphous active agent dispersed in the non-amorphous polymer polyethylene oxide, the Ignatious, Pendyala and Hale patent documents do not teach electrospinning stable amorphous forms of an active agent in a amorphous polymeric carrier. The Verreck reference addresses this shortcoming. The Verreck reference teaches pharmaceutical compositions comprising electrospun fibers with diameters as small as 300-500 nM comprising an amorphous form of itraconazole (abstract), a 7-ringed hydrophobic drug with aqueous and 0.1 N HCl solubility estimated at 1 µg/L and 6 µg/L (p. 811, Table 1), and a polymeric carrier, e.g., hydroxypropylmethylcellulose, which the examiner asserts is inherently an amorphous polymeric carrier (see e.g., http://www.britannica.com/EBchecked/topic/1426100/chemistry-of-industrial-polymers/76383/Amorphous-and-semicrystalline), due to the heterogeneous non-repeating structure of the polymer that prevents semi-crystallization during rapid cooling, all of which was confirmed by differential scanning calorimetry (p. 814, Fig. 5) wherein the pharmaceutical compositions demonstrated T_g deviations from calculated values consistent with amorphous formulations (para. bridging p. 813-814); and wherein complete release of a poorly water soluble drug could be achieved and the rate of drug release from different formulations could be tailored to meet the needs of the active agent and the patient population at issue (Fig. 6-8 and para. bridging p. 816-817). More specifically with respect to the stability of the formulations taught by the Verreck reference, and in consideration of the scope of enablement rejection made supra, the

formulations taught by the Verreck reference retain their amorphous character long enough for routine laboratory storage and testing for the properties relating thereto. This is not surprising, since the glass transition temperature of Eudragit L 100-55, like hydroxypropylmethylcellulose has been calculated as more than 100° C (para. bridging 813-814), as evidenced by Mehta (p. 10, Table 2), providing a buffer between typical storage conditions and the expected T_g of active agent-polymeric compositions.

With respect to product-by-process claims 39 and 46, "even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted). In the instant application, product-by-process claims 39 and 46 refer back to process claims indicating that these processes produce formulations "according to claim 1" (see claims 28 and 40).

The motivation to combine the Pendyala patent document with the Ignatious patent document resides in the teaching in the Pendyala patent document that an active agent's release profile can be tailored and optimized through the use of polymeric carriers such as methacrylic acid - ethylacrylate co-polymer (Eudragit L 100-55), which can improve pharmacokinetic parameters, patient compliance and pharmacodynamic results with active agents. The motivation to combine the Hale patent document with the Ignatious patent document resides in the teaching in the Hale patent document that

brecanavir possesses a two-to-three orders of magnitude advantage in HIV antiviral activity over a number of clinically approved HIV protease inhibitors. The motivation to combine the Verreck reference with the Ignatious patent document resides in the teachings in the Verreck reference that through the use of certain polymers, with favorable glass-transition temperatures and structural heterogeneity, one can not only electrospin poorly soluble active agents into polymeric carriers, but that it is possible to produce electrospun fibers comprising amorphous formulations, and that these electrospun formulations can be further processed, tailoring them to the particulars of the dosage form desired. As such, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to formulate pharmaceutical compositions comprising active agents with low solubility, e.g., the brecanavir taught by Hale, utilizing the combined teachings of Ignatious and Verreck with respect to electrospun fibers and the teachings of Pendyala with respect to methacrylic acid – ethylacrylate co-polymer (Eudragit L 100-55) to produce the amorphous pharmaceutical compositions of claims 1, 3, 6, 8-13, 15-22, 24, 39 and 46 with a reasonable expectation of success. One would have expected of a benefit from this combination due to the variety of possible dosage forms and the opportunity to tailor the release profile of the active agent, e.g., the powerful protease inhibitor brecanavir, enhancing its dissolution, bioavailability and therapeutic response and reducing its dosing frequency and any local side effects by maintaining active agent concentrations within narrow therapeutic windows, with the opportunity to selectively elicit desired therapeutic benefits over an extended period of time when compared with conventional dosage forms.

Claim Disposition

Claims 1, 3, 6, 8-13, 15-22, 24, 39, and 46 are rejected at this time. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to WELDON P. PHILLIPS JR. whose telephone number is (571)-270-7673. The examiner can normally be reached Monday through Thursday between 8:30 AM and 7:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached at 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/WP/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614